

Reference Point

Knowledge gaps impacting the development of bovine viral diarrhea virus control programs in the United States

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Infections with BVDVs result in major economic losses for beef and dairy producers worldwide.¹⁻⁶ The success of control efforts in Scandinavia⁷⁻⁹ has led to a consensus that BVDV eradication in Europe is a realistic goal.¹⁰⁻¹⁴ However, European researchers report that it is not possible to take a 1-size-fits-all approach to the design of eradication programs for different countries.¹⁴ Program design would vary depending on the incidence of BVDV infections, density of animal populations, movement of animals, contact of cattle with wildlife populations, level of producer compliance, and variation among circulating BVDV strains. Current control efforts in the United States focus on the detection of PI animals and are market driven by producers rather than being government mandated. These measures typically target removal of animals that are PI with BVDV from a herd or production unit rather than systematic reduction of the prevalence of BVDV infections. Although beneficial to the participating producers, the cost of animal removals is continuous from year to year because the procedure eliminates PI cattle from individual production units but does not result in the elimination of BVDV from regional cattle populations or the so-called national herd. There is much discussion among researchers and producers as to the feasibility of BVDV eradication from US cattle populations. Eradication is defined as "The purposeful reduction of specific disease prevalence to the point of continuous absence of transmission within a specified area by means of a time limited campaign."¹⁵ Thus, although the voluntary control measures now in effect are associated with the costs of continuous testing of herds,

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ABBREVIATIONS

BVDV	Bovine viral diarrhea virus
BVDV1	Bovine viral diarrhea virus type 1
BVDV2	Bovine viral diarrhea virus type 2
NWC	New World camelid
PI	Persistently infected

eradication would involve a time-limited investment. The question facing the United States is whether this investment is practical and cost-effective. Providing the information necessary to answer this question will require research efforts aimed at elucidating the economic effect of BVDV infections, establishing the efficacy of available vaccines and diagnostic tests, determining the impact of BVDV infections in wildlife, and defining motivations and obstacles affecting producer compliance. The present review is not intended to be a complete account of all knowledge gaps that exist in the study of BVDV but instead focuses on the knowledge gaps that are most important to the evaluation of the need for and the design of comprehensive BVDV control or eradication programs in the United States.

Background Information Regarding BVDVs

Bovine viral diarrhea virus is actually an umbrella term for a highly heterologous group of viruses within the Pestivirus genus of the Flavivirus family.¹⁶ There are 2 distinct species of BVDV (designated as BVDV1 and BVDV2), 2 distinct biotypes (cytopathic and noncytopathic), 2 states of infection (acute and persistent), and 5 clinical forms of acute disease¹⁷⁻¹⁹ (acute BVDV infection, severe acute BVDV infection, hemorrhagic BVDV infection, acute BVDV infection-bovine respiratory tract disease, and acute BVDV infection-immunosuppression). Persistent infection with a noncytopathic BVDV followed by an acute infection with a cytopathic BVDV results in mucosal disease.²⁰

Acute infections may result in enteric, respiratory tract, or reproductive tract disease of varying severity, depending on the viral strain, the immune and reproductive status of the host, and the presence of secondary pathogens. Disease severity ranges from subclinical to fatal. Acute infections of naïve animals of all ages may result in transient diarrhea or pneumonia. In addition, acute forms of the disease may be associated with high mortality rates; these are often, but not always, as-

sociated with a hemorrhagic syndrome. However, most infections are mild and are not important clinically. In pregnant cattle, infections of the fetus may result in abortions, stillbirths, teratogenic effects, or persistent infection. Persistently viremic animals may be born weak and unthrifty or may appear to be healthy calves. Some of these animals may later develop mucosal disease with anorexia, gastrointestinal erosions, and profuse diarrhea, which lead invariably to death.²¹

Although it is denoted as a pathogen of bovids, BVDV will also infect many species of domestic and wild ruminants and pigs.²²⁻²⁴ Bovine viral diarrhea viruses are classified into cytopathic and noncytopathic biotypes on the basis of their activity in cultured epithelial cells.²⁵ Noncytopathic BVDVs predominate in nature. Acute infections with BVDV are always accompanied by immune suppression because, at least in part, of the death of immune cells within lymph nodes and gut-associated lymphoid tissue and a reduction of the number of circulating WBCs.²⁶⁻²⁸ Suppression of the immune system leaves infected animals vulnerable to development of secondary infections. In addition to acute infections, noncytopathic BVDV strains may establish lifelong infections.²⁹ These persistent infections are the result of fetal exposure to BVDV before the development of the immune system. Persistently infected animals that become superinfected with cytopathic BVDV may develop mucosal disease. Cattle that are PI are thought to be the major vector for introduction of BVDV into herds. For this reason, most control programs in the United States focus on the detection and removal of PI animals.

Predicted Return on Investment of a US BVDV Eradication Program

To determine whether the economic benefits of eradication outweigh the expense, it is necessary to first determine the true cost of BVDV infection among cattle to producers. Several different approaches, varying from linear modeling to cost analysis based on direct observation, have been used to estimate the cost of BVDV infections (Appendix).^{3,30-35} Most of the published study data^{3,30-34} are based on estimated costs in dairy production units, with very little information available relating to feedlot, stocker, and beef cow-calf operations. Furthermore, most of these cost estimates are based on data gathered from production units in countries other than the United States. The exact quantification of production damages is difficult because of the number of variables that need to be included in the analysis. These include the cost factors associated with BVDV infections such as reduced milk production, high somatic cell counts (which decrease milk prices), reduced conception rates, immunosuppression that results in increased susceptibility to and increased severity of secondary infections, treatment costs, deaths, and decreased efficiency of feed conversion. Models that neglect any of these factors will underestimate the true cost of BVDV exposure. Direct assessment of production costs in the absence and presence of BVDV infection must account for previous exposure to BVDV (ie, natural exposure or via vaccination), and researchers must be fastidious in testing and controlling for contact

of naïve cattle directly with PI animals or indirectly via contaminated transport, penning, equipment, or feed and water.³⁵ Studies need to be performed to determine the impact of introducing a PI animal into a susceptible herd versus the impact of introducing a PI animal into a vaccinated herd. Such studies would determine the economic benefit of herd immunity.

Epidemiological factors such as risk of exposure, number of naïve animals, and levels of herd immunity are largely undetermined for US production units. Although there are several studies³⁶⁻⁴¹ that detail surveillance for PI cattle in North America, it should be noted that the incidence of PI is not equivalent to the incidence of infection. Although the ratio of persistent to acute infections is unknown, it can be assumed to be small because PI animals are a result of infection of only a proportion of naïve animals during a very narrow period of their life span. The establishment of persistent infection in cattle is a relatively rare event and is a result of fetal infection following acute infection of a susceptible female prior to the first 125 days of gestation or the even rarer event of the impregnation of a PI female. Acute infections of susceptible males, nonpregnant females, and pregnant females after 125 days of gestation are not reflected in the incidence of persistent infection in cattle. A calculation of true incidence of infection must include data relating to both acute and persistent infections.

In addition, variation in BVDV strain virulence will also impact the cost of outbreaks. In Canadian dairy herds, the cost estimate calculated on the basis of relatively mild clinical signs that develop following infection with most BVDV strains was US \$40.60/cow.³³ However, the cost estimate of an outbreak of highly virulent BVDV that occurred in Canada was US \$40,000 to \$100,000/herd.⁴² Furthermore, the control of outbreaks of highly virulent BVDV must be managed differently from outbreaks of less virulent BVDV because of differences in the shedding and spread of virus.⁴³⁻⁴⁵

Although the economic impact gives an impression of the importance of the disease, the cost of control measures must also be factored in to determine the practicality of BVDV eradication. The cost of control or eradication will depend on the approach taken, regional differences in herd size, and type of production predominating in a region as well as BVDV prevalence.⁴ To the authors' knowledge, no estimates of the possible cost of a US BVDV eradication program have been published to date. To determine the cost-benefit ratio for BVDV control in the United States, data are required regarding the prevalence of both acute and persistent infections, the costs incurred as a consequence of BVDV infections in US beef and dairy production units, and the costs that would be associated with control or eradication of BVDV from US herds.

Impact of Variation Among BVDV Strains on Effectiveness of Currently Available Vaccines and Diagnostic Tests

As mentioned previously, BVDVs are segregated into 2 different species within the pestivirus genus: BVDV1 and BVDV2.⁴⁶ Although this segregation was first based on phylogenetic analysis,^{47,48} subsequent characteriza-

tion of viral strains from the 2 species revealed antigenic differences.⁴⁸ The practical importance of antigenic differences was evidenced by the failure of vaccines that were based on BVDV1 strains to control infections with BVDV2 strains in cattle.^{49,50} Furthermore, phylogenetic analysis has revealed subgenotype groupings within the BVDV1 and BVDV2 species.^{51–53} To date, 12 BVDV1 subgenotypes (BVDV1a, BVDV1b, BVDV1c, BVDV1d, BVDV1e, BVDV1f, BVDV1g, BVDV1h, BVDV1i, BVDV1j, BVDV1k, and BVDV1l)⁵³ and 2 BVDV2 subgenotypes (BVDV2a and BVDV2b)⁵² have been identified. The practical importance of segregation into subgenotypes remains a matter of discussion. It is uncertain whether cross-protection against infection with other subgenotypes is conferred by the immune response to infection with 1 subgenotype and whether reagents in diagnostic tests detect or have comparable sensitivities for detection of all subgenotypes. The prevalent BVDV subgenotypes present in the United States are BVDV1a, BVDV1b, and BVDV2a.^{49,51,54–57} Comparison of prevalence rates in published reports over the past 10 years suggests a shift in relative predominance of those subgenotypes and indicates that most field isolates are BVDV1b. However, most commercially available vaccines and diagnostic tests are based on BVDV1a and BVDV2a strains.

Antigen-based testing methods such as immunohistochemical analyses and antigen-capture ELISA depend on 1 or 2 monoclonal antibodies that target viral proteins. A viral variant that escapes detection by immunohistochemical tests and antigen-capture ELISAs, which are based on the binding of a monoclonal antibody against the viral protein Erns, has been identified.⁵⁸ It is not known how prevalent such variants are. Multiple testing strategies, including polyclonal or pooled monoclonal antibodies that detect > 1 viral glycoprotein, may be necessary to detect all PI calves.

In addition to tests that identify all BVDV species and subgenotypes circulating in the United States, there is a need for tests that differentiate each of the 2 BVDV species from other species of pestiviruses. Tests that are able to distinguish each BVDV species from other pestiviruses are necessary because infection of cattle with other pestivirus species may result in clinical signs that mimic those associated with BVDV1 or BVDV2 infection. Conventional wisdom up until the early 1990s was that there were only 3 species in the *Pestivirus* genus: BVDV (types 1 and 2), border disease virus, and classical swine fever virus. Phylogenetic analysis performed in the late 1990s revealed that a virus isolated from a giraffe in 1969 was another species of pestivirus.⁵⁹ Since 2000, 3 additional species have been identified; in chronological order of identification, these are HoBi (first isolated from fetal bovine serum originating in Brazil),⁶⁰ pronghorn (isolated from a pronghorn antelope in the United States),⁶¹ and Bungowannah (isolated from pigs in Australia).⁶² Infections with 2 of the new species (giraffe and pronghorn) have not been associated with any clinical disease outbreak. The Bungowannah species was isolated following a single outbreak that was confined to 2 production units owned by 1 company. In contrast, infection with the HoBi species has since been detected in cattle that originated from both South America and Southeast

Asia.^{60,63} In dairy cattle in Thailand, HoBi virus infection was associated with clinical signs (reproductive tract disease and persistent infection) that mimicked the signs of BVDV1 or BVDV2 infection.⁶³ Because the clinical signs of those infections are similar, it was proposed at the 2008 European Society for Veterinary Virology Pestivirus Meeting that the HoBi species be renamed BVDV3. On the basis of phylogenetic and antigenic differences, it is probable that diagnostic tests designed to detect BVDV types 1 and 2 and vaccines used to prevent BVDV1 and BVDV2 infections and related illnesses will not be effective against the HoBi species.⁶⁰ Introduction of the HoBi species into US cattle herds would have serious consequences for BVDV control programs. To control the potential spread of the virus and its host range, further research needs to be done to determine the prevalence of HoBi, assess the usefulness of available diagnostic tests for detection of the virus, and evaluate the effectiveness of current BVDV vaccines against this emerging pathogen.

Without doubt, there is a need to clearly delineate variations that exist among BVDV strains circulating in the United States and determine whether those variations contribute to diagnostic and vaccine failures. Furthermore, it is important that vigilance be maintained to identify new (emerging) or reemerging BVDV or pestivirus strains that may not be detected by available diagnostic tests and against which current vaccines may be ineffective.

Impact of BVDV Infections in Wildlife and Nonbovine Domestic Species

Although most commonly associated with cattle, the replication of BVDV (determined via virus isolation and serologic analyses) occurs in a wide variety of domesticated and wild ruminants, including cervids such as white-tailed deer, mule deer, fallow deer, elk, red deer, roe deer, eland, and mousedeer.^{64–76} Infection of white-tailed deer with BVDV results in clinical signs similar to those that develop in BVDV-infected cattle.^{77,78} Persistent infection, resulting from natural infection, has been identified in white-tailed deer,^{64,65} mousedeer,⁶⁶ and eland.⁷⁶ Persistent infection in deer has been established through experimental infection of does in the first third of gestation.^{79,80} To the authors' knowledge, studies have not been performed to determine the exact window of vulnerability for development of PI cervids. Although PI cervids have been identified, not much is known regarding their prevalence or survival in the wild. Transmission between PI cervids and cattle has been reported⁸¹; however, there is little information regarding transmission between acutely infected cervids and cattle. The efficacy of vaccination in preventing BVDV transmission among deer and between deer and cattle is not known. Management of cattle exposed to wild cervids infected with BVDV or exposed to virus shed from PI deer will be a critical control point in any BVDV control program in the United States.

Until recently, BVDV infection in NWCs (eg, alpacas and llamas) was considered of limited importance. Although serologic evidence indicated exposure of NWCs to BVDV, prevalence of the virus in NWC populations

appeared to be low, and no clinical disease was associated with exposure.⁸²⁻⁸⁶ Data indicated that BVDV did not cause fetal infections or establish persistent infections in llamas.⁸⁶ It was thought that NWCs were resistant to BVDV infection or that if BVDV infections did develop in NWCs, they were rare and resulted from contact with cattle with little or no transmission of virus among NWCs. This dogma was called into question in the report⁸⁷ of the isolation of BVDV from a stillborn alpaca in 2002. Subsequently, several researchers reported the identification of crias PI with BVDV.^{24,88-91} On the basis of those reports, it became evident that some strains of BVDV readily infected alpacas, that those strains were transmitted among alpacas, and that PI alpacas could be a vector for introduction of BVDV into naive alpaca herds. High genetic similarity among the BVDVs isolated from those outbreaks suggests that the increase in the number of PI alpacas detected is not a result of increased transfer of BVDV from cattle to alpacas but rather a result of the adaptation of a few BVDV strains to improved replication in alpacas.⁹² To date, these new BVDVs do not seem to be widely dispersed among alpaca populations. However, there are concerns that if a BVDV control program is not instituted in alpaca production units, these strains may become more widespread. Knowledge gaps impacting decisions regarding the need and implementation of control programs in alpaca populations include determining the prevalence of BVDV infections in alpacas, the sensitivity and specificity of tests designed for use in cattle when used to detect BVDV infection in alpacas, and the need for and efficacy of vaccines against BVDV for use in alpacas.

Research efforts are needed to investigate the efficiency and likely routes of transmission of BVDV between cattle and other ruminants, both wild and domestic. The need for and design of control programs for nonbovine species should be determined. For nonbovine species, detection of BVDV infections through application of testing techniques presently used in cattle and control of infections via administration of currently available vaccines need to be evaluated.

Improvement of Vaccine Efficacy

Before determining whether vaccine efficacy can be improved, one needs to have an acceptable method for assessment of efficacy. There are 2 goals for BVDV vaccination that are reflected in 2 different label claims that may be pursued in licensing BVDV vaccines.⁹³⁻⁹⁵ One goal is to prevent clinical disease following exposure to BVDV; the corresponding label claim for licensure indicates that the vaccine aids in prevention or reduction of BVDV disease. The BVDV disease referred to in that label claim is not defined as respiratory tract, enteric, or reproductive tract disease. A good experimental method for assessment of efficacy involves a challenge system that results in clear and easily measurable effects that are directly associated with reduced animal health. In practice, clinical signs (pyrexia, diarrhea, and nasal discharge) or factors associated with immunosuppression (leukopenia) or hemorrhaging (thrombocytopenia) are used as criteria for reduction in animal health following BVDV exposure.^{96,97} However, in field settings, BVDV infections are associated with pneumonia and abor-

tion.^{6,42,98-101} At present, there are no model systems that reproducibly replicate BVDV-associated pneumonia or abortion in cattle under experimental conditions. Thus, it is difficult to determine how effective vaccination is in reducing BVDV-associated abortions and pneumonia. Moreover, at this time, there are no universally accepted criteria for determining duration of immunity. Perhaps the most critical goal for a US BVDV control and eradication program is to prevent fetal infections that result in PI fetuses and calves. The vaccine label claim for this goal indicates that the vaccine aids in prevention of fetal infection, including infections that result in PI calves.

Licensing requirements for validation of BVDV vaccine efficacy are currently based on results of clinical trials involving the challenge of vaccinates with a single intranasal inoculation of a BVDV field strain. However, under field conditions, animals are more likely to be exposed over an extended period via commingling with a PI animal. Studies need to be done to compare the 2 challenge methods.

Little information regarding the nature of the immune response that protects against BVDV infection or the levels of protection that are required to prevent either acute disease or fetal infection is available. Results of serologic analyses in calves indicate that a reciprocal titer of 16 is required for reduction of BVDV-associated clinical disease, whereas a titer > 256 is required to prevent systemic spread of virus.¹⁰² The neutralizing antibody titer and the nature of the immunity required for fetal protection are unknown. Although protective B-cell immune responses have been studied more frequently, it is known that T-cell-based immune responses are protective.¹⁰³⁻¹⁰⁵ Only limited comparisons of T- and B-cell responses to BVDV vaccination are available. Further research needs to be done to determine protective levels of immunity and to examine means of manipulating the 2 types of immune responses to provide long-lasting protection that is broad enough to protect against all circulating genotypes and subgenotypes of BVDV.

The most effective vaccination strategies for use in neonates, breeding herds, production units in which stocker calves and replacement heifers are raised, and feedlot situations should also be determined. These strategies need to take into account maternal antibody interference and stressors that reduce an animal's ability to respond to vaccination, differences in immune response related to age and pregnancy status, periods of greatest vulnerability to infection, and negative outcomes of infection. The cost of postvaccinal decrease in milk production or reduced rate of gain must be weighed against the risk and cost of infection.

Thus, to design efficient control programs, it is necessary to understand which immune responses are required for protection, the level of immune response that is effective, and how to best elicit this protective response in vulnerable animals.

Development of More Rapid, Less Expensive, or More Effective Methods of Screening for PI Animals

The failure rates of conventional tests in the field are poorly defined, as are the reasons for test failure. There is controversy regarding both the rate of detec-

tion of acutely infected animals versus PI animals and the rate of test failure introduced by pooling of samples. Further investigations of the most effective testing strategies for dairy herds, beef breeding herds, sale barns, and feedlots are required. Furthermore, the positive and negative predictive values have to be calculated for any test that might be used in control programs. Unlike sensitivity and specificity calculations, the positive and negative predictive values not only depend on the intrinsic accuracy of the test but are also directly proportional to the prevalence of the disease or pathogen to be detected. The positive and negative predictive value calculations are particularly critical for tests used to detect a low-prevalence event such as persistent infection with BVDV. If the prevalence of the disease is very low, the positive predictive value will not be close to 1 even if both the sensitivity and specificity are high. Thus, screening populations that have a low disease prevalence will inevitably lead to a relatively high ratio of false-positive to correct positive test results.¹⁰⁶ Such false-positive results adversely affect the confidence within the constituent groups (ie, the cattle owners, veterinarians, and diagnostic laboratory personnel) implementing a control program. Animals with false-positive test results are typically managed mistakenly as PI cattle, and there are major economic consequences when these animals are removed from production or euthanatized. Animals with false-negative test results have an even greater negative impact on control programs. The potential for even 1 unidentified PI animal to cause considerable adverse economic impact is illustrated by data that indicate that the infection rate among cattle exposed to a PI animal is 70% to 100%.^{107,108}

The need to differentiate animals that have serum neutralizing antibodies attributable to vaccination from those that have serum neutralizing antibodies attributable to natural exposure is becoming more imperative. As stated previously, BVDV infection control programs in the United States are market driven. The participation of producers is predicated on a market bonus. In addition to savings realized through elimination of PI animals, there may also be a premium paid for cattle that are known to be free of BVDV persistent infection and have protective antibodies as a result of vaccination. Cattle with these characteristics are considered a result of good management and are worth a premium price. Other animals on the market are known to be free of BVDV persistent infection and have protective antibodies as a result of natural exposure to BVDV. Findings of 1 study¹⁰⁹ suggest that cattle born with serum anti-BVDV antibodies as a result of in utero exposure after 125 days of gestation have a 2-fold higher rate of severe clinical illness during the first 10 months after birth, compared with cattle that were not exposed in utero. Cattle that have vaccine-induced anti-BVDV antibodies and have not been exposed naturally to BVDV are an indicator that management practices are in effect at the given production unit to protect animals from BVDV infection and are successful in preventing the introduction of BVDV into the production unit. An animal that is naturally exposed to BVDV reflects the failure of management to prevent ingress of BVDV to the production unit. Differentiation of animals that are naturally exposed from those that are

vaccinated allows assessment of the effectiveness of biosecurity practices and could also be used in the identification of value-added animals.

Development of improved test methods needs to be undertaken with an understanding of the production setting in which tests will be used. There is typically a trade-off between cost, sensitivity, and speed of the test; the weighted importance of these 3 factors will vary depending on production unit. Thus, there may not be 1 test that is perfect for use under all circumstances. For example, the importance of chute-side or on-site testing varies by type of production unit. Smaller production units in which the likelihood of transport of animals between sample collection and determination of results of testing is limited and in which the sorting of individual animals is simple do not have a high need for chute-side or on-site testing. In contrast, obtaining the results of testing quickly is important to production units with large populations of animals, units in which access to animals is limited, or units in which animals will be sold or transported soon after testing. Similarly, the cost-risk ratio between the cost of testing and the cost of missing a PI animal will vary by production unit. A cheaper, less sensitive test may be cost-effective and risk acceptable in a feedlot situation in which there are no future generations that will be impacted by overlooking a PI animal. The same test may not be acceptable from a cost-risk standpoint for a breeding herd operation in which the failure to eliminate a PI animal may result in reproductive losses for future calving seasons. Thus, there needs to be more research devoted to fine-tuning tests to be used in different production settings.

Surveillance programs are vital to BVDV control programs because they contribute to the elimination of PI animals. They are also important in that they allow the determination of prevalence of BVDV infection, which in turn contributes to the determination of the costs of BVDV infection. To improve surveillance programs, we need to know the reasons for failure of tests and testing protocols, understand the limits of tests (positive and negative predictive values), and customize testing protocols for different production settings.

Immunosuppression Associated with BVDV Infection in Cattle

To determine the true impact of BVDV infections and to better quantitate the virulence of BVDV strains, the nature of the immunosuppression associated with BVDV infections needs to be clearly understood. Little information is available regarding deficits in immune function—beyond immunotolerance—in PI animals. Similarly, although transient immune suppression following acute BVDV infection has been reported,^{110,111} the mechanisms involved in this suppression, the duration and extent of recovery, and the development of long-term effects, especially in neonates, are still a matter of speculation.

Although immune function is impaired in animals that are born PI with BVDV because of in utero infection prior to 125 days of gestation, little is known regarding immune deficits that result from in utero exposure to BVDV after 125 days of gestation. Epidemiological data

suggest that cattle exposed in utero after 125 days of gestation have an increased incidence of disease.¹⁰⁹ The potential effects of in utero exposure after 125 days of gestation are gaining in importance because the practice of vaccinating pregnant cattle with modified-live virus vaccines is becoming more widespread. A better understanding of the nature of immunosuppression associated with BVDV infection will contribute both to better estimates of the cost of BVDV infections and to the design of BVDV control programs.

Strategies for Improving Producer Compliance for BVDV Infection Control Programs

By definition, compliance of producers is not mandated in voluntary control programs, and there will always be a proportion of producers who choose not to participate. Because the risk of BVDV infection in a region is a function of the number of production units that have BVDV-infected cattle in that region, the success of a regional control program will depend on the participation of most producers in that region. Thus, defining the motivations to participate and, conversely, the obstacles and attitudes that decrease participation is important. Surprisingly, a study^a of producer participation in a voluntary BVDV control program in France revealed that knowledge and understanding of BVDV were not associated with compliance. In that study, understanding of BVDV was generally poor in both enrolled and nonenrolled producers. Factors that affected participation were the farmers' professional and social networks, perceived responsibilities toward their farms and the welfare of animals under their care, understanding of potential losses attributable to the virus, and expected efficiency of control measures. On the basis of those data, it was suggested that compliance is improved when producers are provided with a consistent set of recommendations, tools to assess losses resulting from the introduction of BVDV or its persistence in a production unit, means to identify or measure short- and long-term benefits of infection control as programs progress, and training in biosecurity practices. It appears that the major research gaps regarding control program compliance include determining those factors that affect enrollment in voluntary control programs and defining those tools that contribute to successful and sustained voluntary compliance.

Overview

The purpose of this report was not to promote or discourage the initiation of BVDV control programs. This review does not represent a complete accounting of all knowledge gaps that exist in the study of BVDV infection and control but rather focuses on those knowledge gaps that the authors consider to be the most important in evaluating the need for and the design of comprehensive BVDV control or eradication programs in the United States. None of the knowledge gaps discussed are insurmountable, and in many instances, research that will address the issues brought forward is ongoing. The authors' purpose in writing this review was to help focus and expedite the research community efforts to generate

information that is useful in making decisions regarding BVDV infection control. Furthermore, many of the issues affecting the design of BVDV control programs will be applicable to the control of other diseases of veterinary importance. Regardless of the pathogen involved, pathogen control programs require the development of means to evaluate the cost of the disease versus the cost of control, methods to evaluate vaccine and diagnostic test efficacy that reflect performance in the field, and strategies to improve producer participation in control programs.

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Appendix appears on the next page.